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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/769,144

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Tibor Keler

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EXAMINER

KIM, YUNSOO

ART UNIT

PAPER NUMBER

1644

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PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/769,144	KELER ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	YUNSOO KIM	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 11 February 2010.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 33-36,39-41,44,48-52,55,56,59 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 33-36,39-41,44,48-52,55,56,59 is/are rejected.
- 7) ☒ Claim(s) 41,44 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                       | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>2/11/10,6/3/10</u>  | 6) <input type="checkbox"/> Other: _____                          |

### **DETAILED ACTION**

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/11/10 has been entered.
2. Claims 33-36, 39-41, 44, 48-52, 55, 56 and 59 are pending and are under consideration.
3. Applicant's IDS filed on 2/11/10 and 6/3/10 have been acknowledged.
4. Inquiry to confirm the withdrawal of rejection under 35 U.S.C. 112 first paragraph is acknowledged. The prior office action mailed on 9/22/09 (section 3) indicates the rejection under 35 U.S.C 103(a) is the remaining rejection in light of the amendment filed on 5/21/09. Therefore, the rejection under 35 U.S. C. 112 1<sup>st</sup> paragraph set forth in the office action mailed on 11/21/08 (sections 5-7) has been withdrawn on 9/22/09.
5. In light of the claim amendment filed on 2/11/10, the following new objection has been set forth.
6. Claim 41 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Note that the claim does not refer back in the alternative and claim does not refer to a preceding claim.

Claim 44 is objected to under 37 CFR 1.75(c) as being in improper form because of a multiple dependent claim 41. See MPEP § 608.01(n). Current patent examining practice states that claim 44 should not be further treated on the merits.

However, given that claims 41 and 44 had been examined previously and the remaining rejection is still applicable to the above mentioned claims, claim 44 remains under consideration to advance prosecution. Appropriate correction is required.

7. The following rejection remains.

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 33-36, 39-41, 44, 48-52, 55, 56 and 59 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 01/85798 (IDS reference, of record) in view of U.S. Pat. No. 5,869,057 (IDS reference, of record) for the reasons set forth in the office action mailed on 9/22/09.

The '798 publication teaches a method of inducing an immune response by contacting antigen presenting cells (APC), particularly dendritic cells (DC), with a composition comprising a molecular conjugate (i.e. complex) of a human monoclonal antibody conjugated to a tumor antigen (p. 5-6, 54-55, claims, 33-42, see entire document, particularly the abstract, pages 2, 5-6,

8, 43, 53-57, and claims 33-42) and methods of inducing immune response by administering the composition comprising the molecular conjugate.

The '798 publication also discloses a monoclonal antibody that binds to the macrophage mannose receptor present on DC, and that such antibodies are desirable for practicing the methods disclosed in the '798 publication (see particularly claims 5 and 34). The conjugates of the '798 publication are disclosed as being formed in various ways, including as fusion proteins produced recombinantly (see particularly pages 5, 44, 54, 55). The antibodies used in such conjugates are disclosed as being human, humanized, chimeric and antigen binding fragments such as Fab and scFv (see particularly pages 36 and 39). Notably, the '798 publication teaches the antibody comprising SEQ ID NOs:4 and 8 recited in the instant claims (see particularly Fig. 13, B11 V<sub>L</sub> and B11 V<sub>H</sub> proteins). Note that the recited SEQ ID NOs:4 and 8 encompass the CDRs identified as in SEQ ID NOs:13-18 in claim 41.

Moreover, the '798 publication teaches *in vivo* and *ex vivo* internalization of the antibody-antigen by APC which leads to the generation of immune responses mediated by MHC-I/II complexes including the elicitation of CD4+, CD8+ and cytotoxic T cells ( see particularly pages 5-6, 26, 35, 36, 38-41, 56-58 and claims 5, 16, 23-27, 32, 38-42).

The disclosure of the '798 publication differs from the instant claimed invention in that it does not teach the use of  $\beta$ hCG as an antigen as is currently recited in claims 33, 50 and 59 of the instant application.

The '057 patent teaches the use of  $\beta$ hCG as an antigen that is detectable on 74 different cancer cell lines (see entire document, particularly col. 3, lines 40-50, and col. 5, lines 32-60). The '057 patent further teaches that the  $\beta$ hCG is expressed and is detectable on the surface of tumor cells and could be used in immunization against  $\beta$ hCG and an antimetastasis treatment. Given that the '057 patent teaches the preclusion of additional adjuvant (col. 11, lines 47-64), it meets the limitations of the currently amended claims of 33, 50 and 59.

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Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to employ  $\beta$ hCG as a tumor antigen as taught by the '057 patent in the molecular conjugate comprising a human monoclonal antibody that binds to dendritic cells and immunostimulatory cytokine taught by the '798 publication to practice the claimed method.

One of ordinary skill in the art would have been motivated to do so because of the well known characteristics of  $\beta$ hCG as a tumor antigen in treatment and its availability on many known tumor cells as taught by the '057 patent (col. 3, col. 5, in particular).

From the teachings of references, it would have been obvious to one of ordinary skill in the art to combine the teachings of the references and there would have been a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time of invention was made, as evidenced by references, especially in the absence of evidence to the contrary.

Applicants' arguments filed on 2/11/10 have been fully considered but they were not persuasive.

Applicant has asserted that the combination of the references does not teach or suggest "(composition) formulated without an adjuvant or immunostimulatory agent" and it would not have been obvious that  $\beta$ hCG could be used as a vaccine to induce T cell mediated immune response. Applicant has further asserted that the  $\beta$ hCG based vaccine requires an adjuvant and a carrier while the claimed composition does not require such adjuvant. Applicant has asserted that a number of references (Gupta et al., Triozzi et al., and Lund et al.,) discloses that the additional adjuvant or protein carrier is required when  $\beta$ hCG is used as an antigen.

However, Applicant's assertion based on the  $\beta$ hCG needs to be conjugated to toxin moiety (response filed 2/11/10, p. 7) in the presence of muramyl dipeptide (e.g. adjuvant) or protein carrier is misleading. Applicant submits Gupta et al., Lund et al., Dalum et al., and Triozzi et al. references as basis for this assertion. It is noted that the  $\beta$ hCG used in the Triozzi et al. reference is from carboxyl end of hCG (the first 37 amino acids). Lund et al. reference (also provided by

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Applicant) clearly discloses that the 37 amino acids from carboxyl terminus of  $\beta$ hCG requires immunogenic carrier protein while the holo-  $\beta$ hCG hormone does not require any adjuvant. Moreover, Lund et al. teach that the purified  $\beta$ hCG in the absence of carrier protein elicits immune response (p. 71, under T cell epitope). Based on the references provided by Applicant, only carboxyl end of hCG may elicit more potent immune response in the presence of carrier protein. The claimed  $\beta$ hCG is derived from SEQ ID NO:20 as is defined by the specification of the instant application in p.12. The claimed  $\beta$ hCG is outside of the carboxyl terminus (e.g. 1-37 amino acids) that is corresponding 61-69 of the entire hCG. Thus, Applicant's assertion based on the segment of hCG that is not recited in the claimed invention is irrelevant.

Further, Applicant's assertion based on the requirement of additional protein carrier molecule when the  $\beta$ hCG molecule is used is misleading. Applicant has asserted that Gupta et al., Triozzi et al., Dalum et al. and Lund et al. demonstrated that the protein carrier or helper T cell epitopes is required to render this self antigen to be immunogenic. As discussed above, the carboxyl end of hCG is different from the claimed  $\beta$ hC. Even if the claimed  $\beta$ hCG would require an additional adjuvant, this is achieved by the '798 publication. As discussed above and previously, molecular conjugate taught by the '798 publication binds macrophage mannose receptor on dendritic cells is conjugated to a tumor antigen and this conjugate binds autoantigen (p. 36). Given that this conjugate leads *in vivo and ex vivo* internalization of the antibody-antigen by APC which leads to the generation of immune responses mediated by MHC-I/II complexes including the elicitation of CD4+, CD8+ and cytotoxic T cells ( see particularly pages 5-6, 26, 35, 36, 38-41, 56-58 and claims 5, 16, 23-27, 32, 38-42). Thus, the prior art molecular conjugate in fact acts as a protein carrier and successfully induces T cell mediated immune responses. Given that the prior art molecular conjugate acts as a protein carrier and induces T cell mediated response, the prior art molecular conjugate would be immunogenic when it is conjugated to  $\beta$ hCG.

Note that since the vaccine compositions of the '057 patent are useful because they induce an immune response, and because the '798 publication discloses methods by which immune responses are increased by specifically targeting antigens to the APC which are responsible for

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initiating the immune response, a person of ordinary skill in the art would be motivated to use the constructs of the '057 patent in the molecular conjugate of the '798 publication in order to induce a stronger immune response by virtue of increasing antigen presentation.

As discussed previously, methods which employ a conjugate of antigen and an antibody against MMR to form a molecular conjugate which directly targets the human MMR on APC and induces an immune response mediated by both CD4+ and CD8+ T cells were taught by the '798 publication. The CTL response mediated by CD4+ and CD8+ T cells and MHC-I/II complexes are taught throughout the '798 publication and such immune response are achieved by the molecular conjugation of monoclonal antibody that binds to the macrophage mannose receptor on APC and a tumor antigen. Indeed, beginning on page 54, the '798 publication discloses:

In another embodiment, the methods and compositions of the invention can be used to modulate an immune response in a subject towards an antigen. The human anti-dendritic cell antibodies of the invention can be used to target an antigen to a dendritic cell and thereby modulate antigen presentation and processing, such that an immune response to the antigen is induced. The antigen can be a tumor antigen, or an antigen from a pathogen, e.g., a microbial pathogen. The pathogen can be a virus (e.g., HIV), a bacterium, a fungus, or a parasite. The antigen can also be a component of an amyloid deposit in a patient, such as a patient suffering from Alzheimer's disease and the antigen is A $\beta$  peptide.

For example, a molecular complex comprising at least one binding specificity for a component on the surface of a dendritic cell linked to an antigen, wherein binding of the complex to the dendritic cell mediates internalization of the molecular complex, can be administered to a subject to induce or enhance an immune response against the antigen. The immune response generated against the antigen includes antibodies that bind to the antigen and T cells that bind to the antigen as a component of an MHC-I or MHC-II complex. Accordingly, the human anti-dendritic cell antibodies of the invention can also be used to mediate dendritic cell-targeted immunization of a subject. For example, a subject can be immunized with a molecular complex comprising at least one binding specificity for a component on the surface of a dendritic cell linked to an antigen, wherein binding of the complex to the dendritic cell mediates internalization of the molecular complex, and, for example, enhances processing and presentation of the antigen.

Further, the '798 publication states:



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"bispecific and multispecific molecules of the invention comprises a binding specificity for an antigen on a target cell, e.g. a tumor cell antigen, a microbial antigen, a viral antigen or an autoantigen and a second binding specificity for dendritic cells" (p. 36, lines 22-25) and

"Thus, the antibodies of the invention can be used to stimulate the immune response to pathogens, toxins and self-antigens" (p.55, lines 17-18).

Thus, it is clear that the '798 publication discloses methods whereby a tumor antigen is targeted for efficient uptake and presentation on MHC class I and II molecules via conjugation of the tumor antigen to an dendritic-cell specific antibody. Note that the '057 patent is provided to show the motivation to select the  $\beta$ hCG as a tumor antigen because it is expressed and detectable on the surface of many tumor cells. The '057 patent further discloses that  $\beta$ hCG is to be used for immunization and as an antimetastasis treatment (col. 3, lines 40-50, col. 5, lines 32-60).

Therefore, a person of ordinary skill in the art would have been motivated to use  $\beta$ hCG as the tumor antigen in the methods of generating an anti-tumor antigen immune response that are disclosed in the '798 publication since the '057 patent discloses that  $\beta$ hCG is a tumor antigen that is to be used in vaccines to stimulate an immune response to the tumor antigen, and that  $\beta$ hCG is a particularly desirable tumor antigen to target because it is expressed on a wide variety of different tumors.

Further, the '057 patent discloses generically that  $\beta$ hCG is a tumor antigen. Tumor antigens are self antigens, and as such they all display some degree of "self-tolerance". Note that the '798 publication explicitly states that tumor antigens are to be used. Given that the '798 publication teaches that the molecular conjugate that is capable of inducing T cell response and the '057 patent provides motivation to select  $\beta$ hCG as a tumor antigen, the combination of references provides reasonable expectation of success and predictability to support a conclusion of nonobviousness. See MPEP 2143.02.

Furthermore, Applicant has asserted that the claimed composition requires no adjuvant or immunostimulatory agent. However, the specification of the instant application defines adjuvant

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to include preservatives, wetting agents, emulsifying agent and dispersing agent (p. 30). The exemplary preservatives, wetting agents or emulsifying agent includes polyols, surfactants and the like (p. 30, lines 11-25). Given that the surfactant such as Tween 20 acts as an adjuvant in the vaccine art, the claimed composition does not preclude substances which have multiple properties. Even if the claimed composition precludes any means of adjuvant in the composition, at any stages of treatment, the claimed invention is still obvious over the combination of the prior art. The '057 patent states (col. 11, lines 47-64):

My invention offers four primary advantages over prior art. ...  
Second, my invention precludes the need for additional adjuvants such as muramyl dipeptide in the final vaccine formulation (lines 54-55).

Therefore, the prior art recognizes preclusion of additional adjuvant if self and non-self recognition is established using the antigen such as  $\beta$ hCG and the presence of T cell immune response inducing protein carrier is achieved by the '798 publication. The combination of the references remains obvious and thus rejection is maintained.

10. No claims are allowable.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to YUNSOO KIM whose telephone number is (571)272-3176. The examiner can normally be reached on M-F, 9-5. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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July 1, 2010

/Yunsoo Kim/

Examiner, Art Unit 1644